Abnormal Cardiac Biomarkers in Patients with Systemic Lupus Erythematosus and No Prior Heart Disease: A Consequence of Antimalarials?

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ABSTRACT. ***Objective.*** Cardiac involvement in systemic lupus erythematosus (SLE) is often undiagnosed in its early phases. Specific heart biomarkers may identify patients at risk. We sought to investigate the prevalence and associated factors for such biomarkers in SLE.

Methods. Brain natriuretic peptide (BNP) and cardiac troponin I (cTnI) were measured simultaneously in 151 consecutive patients with no history of heart disease or pulmonary arterial hypertension (PAH). None had electrocardiographic abnormalities suggestive of acute coronary syndrome. Cross-sectional comparisons and logistic regression analyses were performed. Patients with abnormal biomarkers were investigated to delineate the specific cause.

Results. Sixteen patients (16/151, 10.6%) had elevated BNP, and 9 of them also had abnormal cTnI. Compared to subjects with normal biomarkers, they were older, had longer disease and antimalarial (AM) use duration, and more frequently persistent creatine phosphokinase (CPK) elevation. Multivariable regression analysis showed prolonged AM treatment (> 5.6 yrs) and persistent CPK elevation to be important predictors for elevated cardiac biomarkers. Six patients were diagnosed with definite (based on endomyocardial biopsy, n = 2) or possible (based on cardiac magnetic resonance after exclusion of other causes) AM-induced cardiomyopathy (AMIC); all had both BNP and cTnI elevated. Alternative causes were identified in 5, while no definitive diagnosis could be made in the remaining patients.

Conclusion. About 10% of patients with SLE had elevated myocardial biomarkers, in the absence of prior cardiac disease or PAH. One-third of them were diagnosed with AMIC. Prolonged AM therapy and persistent CPK elevation conferred an increased risk for abnormal BNP and cTnI, which might predict AMIC. (First Release August 1 2018; J Rheumatol 2019;46:64–9; doi:10.3899/jrheum.171436)

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Cardiac involvement in systemic lupus erythematosus (SLE) may affect all anatomical structures of the heart. Accelerated atherosclerosis and premature coronary artery disease represent important comorbidities[1]. Occasionally, heart disease may be subclinical and remain undiagnosed, leading over time to heart failure or arrhythmias. In such cases prolonged antimalarial (AM) treatment, subclinical myocarditis, and other factors have been implicated[2].

AM are currently recommended for all patients with SLE who lack specific contraindications[3]. They reduce the rate of clinical flare, damage accrual, and thrombotic manifestations, while they are associated with a favorable metabolic profile and improved survival[4,5,6,7,8]. In large cohorts, about 70% of patients with SLE are using AM for prolonged periods[9]. The most important side effect is retinal damage, whereas neuromyotoxicity and cardiomyopathy have been described in isolated cases[10,11].

AM-induced cardiomyopathy (AMIC) has been reported

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in only 47 patients (19 with SLE) to date. Duration of use and cumulative dose are considered the determining factors[12]. However, given the large number of patients treated with AM for prolonged periods, it seems possible that AMIC is underrecognized. Disease pathophysiology is poorly understood. It has been described as a hypertrophic, restrictive cardiomyopathy with diastolic dysfunction and a high prevalence of conduction abnormalities[12]. It can be speculated that AM deposition in the myocardial fibers will lead to a chronic, subclinical tissue necrosis. If this process is not reversed (after drug discontinuation), hypertrophy and eventually heart failure will occur. In this context, heart-specific biomarkers, such as cardiac troponin (for the assessment of myocardial necrosis) and brain natriuretic peptide (BNP; for the assessment of volume and/or pressure overload) may be of value in identifying subclinical heart damage. The aim of our study was to assess the prevalence of abnormal heart biomarkers in patients with SLE and delineate their relevance, with special emphasis on detecting AMIC.

MATERIALS AND METHODS

Our study included 179 consecutive patients (162 women) attending the University of Toronto Lupus Clinic who were enrolled from March to May 2016. All patients fulfilled the American College of Rheumatology 1997 revised criteria for SLE classification or had 3 criteria plus compatible histopathology (skin or kidney biopsy)[13]. Twenty-eight patients with a history of ischemic heart disease (angina, myocardial infarction, coronary angioplasty, coronary artery bypass graft, atherosclerotic congestive heart failure), significant valvular disease (requiring valvular surgery), and pulmonary hypertension (PH) were excluded from further analysis. At the time of the assessment, none of the remaining 151 patients had chest pain or electrocardiographic (ECG) abnormalities suggestive of acute coronary syndrome (no ST elevation and no change compared to the previous ECG).

High-sensitivity cardiac troponin I (cTnI) and BNP were measured simultaneously in serum and plasma samples, respectively. Measurements were performed shortly after venipuncture with chemiluminescent microparticle immunoassay on an Architect i2000SR analyzer (Abbott Diagnostics). Normal range was < 26 ng/ml for cTnI and < 100 pg/ml for BNP.

Patients (n = 151) were categorized according to normal or abnormal BNP and/or cTnI. Groups were compared for differences in demographic variables, disease and AM use duration, cumulative dose for chloroquine (CQ) and hydroxychloroquine (HCQ), disease activity at the time of assessment (SLE Disease Activity Index 2000), prevalence of abnormal creatine phosphokinase (CPK; defined as 3 or more abnormal measurements during the last 2 years in the absence of active myositis), frequency of glucocorticosteroid and immunosuppressive use, and mean prednisone dose. Differences in the prevalence of arterial hypertension (HTN) along with the actual blood pressure (BP) at the time of assessment and mean BP of the last 4 clinic visits and current use of diuretics were also assessed. Lastly, renal function (based on estimated glomerular filtration rate; eGFR) was also documented.

Patients' demographic, clinical, laboratory, and therapeutic variables, as well as cardiac biomarker levels, were compared using t test for continuous variables and chi-square test for binary variables. For the assessment of the effect of AM duration on abnormal cardiac biomarkers, patients were divided into 2 groups according to the median duration of use, which was calculated at 5.6 years in the current cohort. Multivariate regression analysis for predictors of abnormal heart biomarkers was conducted. A step-down approach was followed with variables being removed until the smallest Akaike information criterion was reached. Statistical analysis was performed with SAS 9.0 software.

All patients have provided written informed consent for studies being conducted in the University of Toronto Lupus Clinic, and the study was approved by the University Health Network Research Ethics Board (UHN/REB: 14-7975 AE).

RESULTS

Sixteen (16/151, 10.6%) patients with no prior cardiac disease were found to have abnormal BNP, of whom 9 (6%) also had abnormal cTnI. In all patients, both tests were confirmed after 3–4 months.

Compared to patients with normal biomarkers (n = 135), those with elevated biomarkers were older, had longer disease duration, and were more frequently hypertensive and using diuretics. Twenty-eight of them had been taking CQ and 137 HCQ during the disease course (14 patients had been treated with both drugs at different time periods). Cumulative years taking AM and prevalence of abnormal CPK were also significantly higher in those with elevated biomarkers. Details are provided in Table 1. Further analysis based on the presence of abnormal CPK (n = 29) or not (n = 122) showed that patients with this abnormality had abnormal BNP more frequently (31.03 vs 5.74%, $p < 0.001$, mean value 186 ± 499 vs 71 ± 266 pg/ml, $p = 0.19$) and cTnI (17.24 vs 2.46%, $p = 0.005$, mean value 23 ± 48 vs 5 ± 11 ng/ml, $p = 0.03$).

Univariable and multivariable regression analyses for identifying predictors for abnormal BNP/cTnI are shown in Table 2. AM use for more than 5.6 years, abnormal CPK, and use of diuretics were associated with increased risk for elevated cardiac biomarkers, while normal eGFR was protective. Of the 16 patients with abnormal BNP/cTnI, 14 were taking AM consistently for more than 5.6 years.

These 16 patients were investigated and followed for the next 12 months to delineate the cause of this abnormality. Six patients (3 with new-onset heart failure) were thoroughly assessed with heart ultrasound and cardiac magnetic resonance imaging (cMRI) and were found to have features highly suggestive of AMIC (biventricular and septal hypertrophy, biatrial enlargement, late gadolinium enhancement in a nonvascular pattern). Five of them were treated with HCQ and 1 with CQ (total duration of AM treatment 20.5 ± 4 yrs). In 2 of them, the diagnosis was confirmed with endomyocardial biopsy (after 13 and 22 years taking AM, respectively). Of note, only 1 patient with AMIC based on cMRI had moderate mitral valve regurgitation; no other valvular disease was detected. Interestingly, 3 of them (including the 2 patients with biopsy-proven AMIC) had reported arterial HTN; however, that was tightly controlled as confirmed by office readings and 24-h ambulatory BP monitoring (that also excluded unrecognized "masked" HTN). One patient died of refractory heart failure with preserved ejection fraction, which was complicated by sepsis during admission to an intensive care unit. Measurements of BNP/cTnI were repeated on a quarterly basis in all these patients for a year after drug withdrawal. In 4 patients, both BNP and cTnI were initially elevated and gradually decreased over time.

Table 1. Comparison between BNP/cTnI abnormal and BNP/cTnI normal patients.

Variables	BNP/cTnI Abnormal, n = 16	BNP/cTnI Normal, n = 135	p
Age, yrs, mean ± SD	54.7 ± 15.1	47.1 ± 12.4	**0.025**
Female	14 (87.5)	125 (92.6)	0.476
Male	2 (12.5)	10 (7.4)	
Ethnicity			
White	10 (62.5)	70 (51.9)	0.393
Black	3 (18.8)	27 (20)	
Asian	3 (18.8)	18 (13.3)	
Other	0	20 (14.8)	
SLE duration, yrs, mean ± SD	22.54 ± 10.44	14.83 ± 9.73	**0.003**
SLEDAI-2K, mean ± SD	1.88 ± 2.47	2.92 ± 3.71	0.276
eGFR, ml/min, mean ± SD	82.7 ± 21.58	117.3 ± 116.4	**0.003**
eGFR < 30 ml/min	0 (0)	3 (2.2)	0.547
Hypothyroidism	2 (12.5)	5 (3.7)	0.114
Hypertension	10 (62.5)	45 (33.3)	**0.022**
Diuretics treatment	5 (31.3)	7 (5.2)	**< 0.001**
Mean systolic BP, mmHg, mean ± SD§	119.58 ± 17.1	113.3 ± 12.9	0.078
Mean diastolic BP, mmHg, mean ± SD§	72 ± 7.6	70.4 ± 8.5	0.486
Systolic BP at test, mmHg, mean ± SD	118.4 ± 21.7	113.2 ± 16.8	0.258
Diastolic BP at test, mmHg	71.9 ± 10.1	69.4 ± 12.1	0.43
Diabetes	0 (0)	7 (5.2)	0.351
Dyslipidemia	4 (25)	30 (20.7)	0.693
Abnormal CPK*	7 (43.8)	22 (16.3)	**0.008**
Ever on AM	16 (100)	126 (93.3)	0.287
Ever on CQ	5 (31.3)	23 (17)	0.167
Ever on HCQ	14 (87.5)	123 (91.1)	0.638
Cumulative dose of CQ, g, mean ± SD	1509 ± 690	900 ± 287	**0.003**
Cumulative dose of HCQ, g, mean ± SD	1251 ± 883	1057 ± 695	0.335
Yrs taking AM, cumulative, mean ± SD	13.66 ± 9.14	7.27 ± 7.51	**0.002**
Taking AM > 5.6 yrs	14 (87.5)	57 (42.2)	**< 0.001**
Corticosteroids	8 (50)	64 (47.4)	0.844
Mean prednisone, mg/day, mean ± SD	9.4 ± 4.2	7.6 ± 5.3	0.374
Immunosuppressives	10 (62.5)	79 (58.5)	0.76

Data are n (%) unless otherwise indicated. Significant data are in bold face. §Mean value of last 4 visits. *Three abnormal measurements during the last 2 years. eGFR: estimated glomerular filtration rate; BP: blood pressure; CPK: creatine phosphokinase; AM: antimalarials; CQ: chloroquine; HCQ: hydroxychloroquine; BNP: brain natriuretic peptide; cTnI: cardiac troponin I; SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000.

Table 2. Univariate and multivariate analyses for assessing predictors of abnormal BNP/cTnI.

Predictor	OR	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Pr > Chi-square
Univariate analysis				
Age at test	1.047	1.002	1.094	0.0413
SLE duration at test	1.064	1.014	1.116	0.0114
eGFR at test	0.973	0.954	0.991	0.0039
Hypertension at test	3.025	1.042	8.776	0.0417
Diuretics treatment at test	8.183	2.288	29.268	0.0012
CPK abnormal	3.951	1.346	11.598	0.0124
Cumulative AM dose	1.105	1.031	1.184	0.0045
Yrs taking AM, cumulative (> 5.6 yrs)	1.069	1.015	1.125	0.0119
Multivariate analysis				
eGFR	0.978	0.957	0.999	0.0362
Diuretics	4.218	1.078	16.503	0.0386
CPK abnormal	4.624	1.221	17.511	0.0242
Yrs taking AM, cumulative (> 5.6 yrs)	5.431	1.14	25.881	0.0337

eGFR: estimated glomerular filtration rate; CPK: creatine phosphokinase; AM: antimalarials; BNP: brain natriuretic peptide; cTnI: cardiac troponin I; SLE: systemic lupus erythematosus.

Table 3. Investigations of patients with abnormal heart biomarkers and no history of heart disease or pulmonary arterial hypertension.

Age/sex	Biomarkers	ECG	TTE	cMRI	Outcome
74/F	cTnI, BNP, CPK	RBBB, LAFB, LQT	LVH, RVH, LA, RA, IVSH, DD, LVEF = 30%	LVH, RVH, LA, RA, IVSH	Heart biopsy was pathognomonic for AMIC. AM discontinuation led to steady decrease of both cTnI and BNP and regression of hypertrophy.
63/F	cTnI, BNP, CPK	RBBB, LAFB	LVH, RVH, LA, IVSH, DD	LVH, RVH, LA, IVSH, LGE nonvascular	Heart biopsy was pathognomonic for AMIC. AM discontinuation led to steady decrease of both cTnI and BNP and regression of hypertrophy.
74/F	cTnI, BNP, CPK	First-degree AVB	LVH, LA, IVSH, DD	LVH, RVH, LA, RA, IVSH	Normal coronary angiography. Patient succumbed from refractory heart failure, complicated with septic shock. Possible AMIC.
59/F	cTnI, BNP	Normal	LVH, IVSH, LA, RA, DD	LVH, IVSH	Regression of hypertrophy and decrease of heart biomarkers after 6 months. Possible AMIC.
49/F	cTnI, BNP, CPK	RBBB	LVH, RVH, IVSH, LA, DD	LVH, RVH, IVSH, LA	Regression of hypertrophy, all biomarkers normalized after 12 months. Possible AMIC.
67/F	cTnI, BNP, CPK	Atrial fibrillation	LVH, LA, IVSH, DD	LVH, IVSH, LA	Possible AMIC, biomarkers at the same levels after 3 and 6 mos (AM not discontinued until later).
49/M	cTnI, BNP	Normal	LVH, LA, IVSH, DD	ND	Coronary artery disease (2 vessels), biomarkers unchanged after 6 mos (AM not discontinued).
57/F	cTnI, BNP, CPK	Nonspecific T abnormality	LVH, IVSH, regional hypokinesis, LVEF = 55%	LVH, LGE nonvascular, edema	Myocarditis. Treatment with cyclophosphamide and glucocorticoids led to regression of edema in cMRI. Partial decrease of biomarkers.
30/F	BNP	Normal, right axis deviation	RVH, RVSP = 69 mmHg	ND	PH. Treatment with phosphodiesterase-5 inhibitors led to normalization of BNP after 6 mos.
38/F	BNP	Normal	Small pericardial effusion, RVSP = 44 mmHg	ND	Patient had nephrotic syndrome owing to active lupus nephritis. Elevated BNP was attributed to volume overload.
71/F	BNP	Possible LVH, incomplete RBBB	LVH	LVH	Uncontrolled hypertension. BNP remained at the same levels despite intensive treatment after 6 and 12 mos. Cardiac troponin was marginal and remained unchanged at the same time.
71/F	BNP	Atrial fibrillation, Possible LA enlargement	LA enlargement, moderate MV regurgitation	LA, LVH	No specific cause identified. BNP remained at the same levels after 6 months. AM dose was decreased.
44/F	BNP, CPK	Possible biatrial enlargement	Mild global hypokinesis of the LV, LVEF = 45%	ND	No specific cause identified. Coronary CT with Agatston score 0. BNP remained in the same levels after 6 and 12 mos.
52/F	BNP	Normal	Normal	Normal	No specific cause identified. BNP remained in the same levels after 6 and 12 mos.
64/F	BNP, CPK	RBBB, possible LVH	Normal	ND	No specific cause identified. BNP remained in the same levels after 3, 6, and 12 mos.
48/M	cTnI, BNP	Nonspecific T abnormality	Normal	ND	No specific cause identified. BNP and cTnI were slightly decreased (still abnormal) after 6, 9, and 12 mos

ECG: electrocardiogram; TTE: transthoracic echocardiogram; cMRI: cardiac magnetic resonance imaging; cTnI: cardiac troponin I; BNP: brain natriuretic peptide; CPK: creatine phosphokinase; RBBB: right bundle branch block; LAFB: left anterior fascicular block; LQT: long QT; LVH: left ventricular hypertrophy; RVH: right ventricular hypertrophy; LA: left atrium dilatation; RA: right atrium dilatation; IVSH: interventricular septum hypertrophy; LVEF: left ventricular ejection fraction; AM: antimalarials; AMIC: AM-induced cardiomyopathy; DD: diastolic dysfunction; LGE: late gadolinium enhancement; AVB: atrioventricular block; ND: not done; PH: pulmonary hypertension; RVSP: right ventricular systolic pressure; CT: computed tomography.

AM withdrawal (5 HCQ, 1 CQ) was the only intervention in 4, while diuretics were concomitantly administered in 2 patients. Of note, 5 of these patients had persistently elevated CPK for many years before AMIC. Four patients underwent genetic testing for α-galactosidase polymorphisms for the exclusion of Anderson-Fabry cardiomyopathy and for familial forms of hypertrophic cardiomyopathy (although they had negative family history); genetic tests were negative in all of them. Details are given in Table 3.

Regarding the remaining patients, a specific diagnosis was made in 5. One was diagnosed with coronary artery disease (both cTnI and BNP were elevated), one with lupus myocarditis (both cTnI and BNP were elevated; diagnosis was based on the presence of edema in cMRI), 2 with PH (1 in the context of nephrotic syndrome; both had only abnormal BNP), and 1 with poorly controlled HTN (only BNP was elevated). Appropriate treatment led to normalization or decrease of heart biomarkers after 6 months.

In the remaining 5 patients (4 with elevated BNP only, 1 with BNP and cTnI), initial investigation with ECG and transthoracic echocardiogram did not reveal any abnormal findings. No specific treatment was offered; cardiac biomarkers remained at the same levels after 3–12 months without AM discontinuation. Of note, their AM use duration was similar to that of the other patients (14 yrs on average). These patients are closely monitored for the timely detection of any cardiac complication. Details on the investigations of these patients are given in Table 3.

DISCUSSION

In our present study, abnormal BNP and/or cTnI were found in 10.6% (16/151) of patients with SLE who had no history of heart disease or PH. Prolonged AM use (> 5.6 yrs) was associated with increased risk for this abnormality, regardless of age and SLE disease duration. Elevations of these biomarkers implicate possible active myocardial necrosis (cTnI) and/or increased intracardiac ventricular pressure (BNP). In this context, AM deposition in the myocardium, leading over time to overt cardiomyopathy, may be an important contributing factor. Indeed, 6/16 of these patients were ultimately diagnosed with definite or possible AMIC, while 3 of them were completely asymptomatic and their investigation was initiated because of the abnormal biomarkers. Precise diagnosis requires the detection of cytoplasm vacuolation and the virtually pathognomonic curvilinear bodies within cardiomyocytes on EMB[12]. Clinical features are those of heart failure. Prognosis is poor, with about 45% mortality[12].

Because duration of AM treatment is the critical predictor of AMIC[2], the majority of patients with SLE should be considered at risk because most of them receive longterm maintenance therapy. Because AMIC develops after many years of AM therapy, patients may eventually present with clinical heart failure, which may be falsely attributed to other cardiac causes with similar morphological changes on non-invasive imaging, such as hypertensive heart disease. Nevertheless, expensive and invasive investigation is unjustified in asymptomatic individuals. Therefore, identification of heart-specific biomarkers for the detection of subclinical heart damage will facilitate stratification of these patients by defining those with the greater risk. In our current study, the selection of biomarkers was based on the hypothesis that AM deposition in cardiomyocytes will lead to necrosis and increase in cTnI. At later stages, necrosis will lead to cardiac dysfunction and BNP elevation, even with minimal or no symptoms.

Our findings are in agreement with this hypothesis. Of the 9 patients who had both cTnI and BNP elevated, 6 were diagnosed with definite or possible AMIC (of the 3 remaining, investigations revealed a diagnosis of lupus myocarditis in 1, coronary artery disease in 1, and unknown cause in 1). Patients who had only abnormal BNP were diagnosed with other causes or there is no definite diagnosis yet.

Concerning the differences in cardiotoxicity between CQ and HCQ, the small numbers do not allow for definite conclusions. It seems, however, that CQ may have an enhanced potential for heart damage based on the finding that its cumulative dose was marginally higher in the patients with abnormal heart biomarkers.

Further, persistently elevated CPK was an important associated factor for abnormal cardiac biomarkers. AM are associated with a peculiar type of myopathy, characterized by the presence of acid phosphatase–positive vacuoles, indicating impaired lysosomal activity[14]; they also induce autophagy by reducing lysosomal enzyme activity[15]. We showed that chronic AM use is associated with a more than 3-fold increased risk for elevated CPK (after excluding patients with active myositis and statin therapy)[16]. In particular, 16% of AM users developed abnormal CPK after 4 years on average and this persisted over time (for 7 yrs on average) in about half of them. Chronic CPK elevation remained subclinical in most patients because myopathy with proximal muscle weakness developed in only 2.5%. It is not known whether elevated CPK may predict patients at risk for development of AMIC or whether certain patients are predisposed to AM-related muscle damage. Based on these observations it can be hypothesized that AM deposition in muscle tissue (expressed with chronic CPK elevation) is not restricted to skeletal muscles; the drugs also accumulate within other types of muscle tissue, such as the myocardium. Nevertheless, not all patients with abnormal CPK had abnormal cardiac biomarkers, and vice versa.

Regarding the possible association of elevated BNP and cTnI with advanced chronic and endstage renal disease[17], none of our patients with abnormal biomarkers had an eGFR < 30 ml/min. In this context, that could not be attributed to renal dysfunction. In addition, diuretics were administered in

5/16 patients as antihypertensive agents and not for heart failure.

Patients with SLE who receive prolonged AM treatment are at increased risk for elevated cardiac biomarkers (BNP/cTnI), particularly when persistently elevated CPK is present. The value of monitoring these biomarkers lies in the early identification of patients with AMIC or other cardiac diseases in subclinical stages and possibly in the detection of patients at high risk for developing such complications in the future. Cardiac biomarkers could become a screening test for patients with SLE using AM for longer than 5.6 years and/or who have persistently elevated CK levels. Further research is needed to delineate the differential toxicity of CQ and HCQ.

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